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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,667	04/05/2005	Vasulinga Ravikumar	ISIS-5582	4970
23377	7590	11/15/2006	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE, 46TH FLOOR 1650 MARKET STREET PHILADELPHIA, PA 19103			VIVLEMORE, TRACY ANN	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/510,667

Applicant(s)

RAVIKUMAR ET AL.

Examiner

Tracy Vivlemore

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 11-23 is/are pending in the application.
- 4a) Of the above claim(s) 19 and 21-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 11-18 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/12/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election of group I, claims 1-18 and 20 in the reply filed on September 18, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5-10 and 24-41 have been canceled. Claims 19-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 18, 2006.

Claims 1-4, 11-18 and 20 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim recites a pharmaceutical composition. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require

Art Unit: 1635

the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism.

The specification describes oligomeric compounds comprising a monothiophosphate at the terminus and the use of these compounds to inhibit gene expression in cultured cells. The specification also provides a prophetic example of the use of these compounds *in vivo*. The specification provides no working examples describing the administration of the claimed compounds to any organism for a therapeutic purpose.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

"Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to use the described oligonucleotides as a pharmaceutical as claimed.

Art Unit: 1635

Therefore, given the teachings of the prior art of the unpredictability of using oligonucleotides as pharmaceuticals and the lack of specific guidance or working examples in the specification describing such use, the instant specification is not enabling for a pharmaceutical composition comprising an antisense oligonucleotide.

This rejection may be overcome by removing the word "pharmaceutical" from the preamble of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 11, 13-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Yau (US 5,210,264).

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at one terminus. Claim 2 recites that Q₁ is S, reciting a thiophosphate attached to a normal ribose sugar. Claim 11 limits claim 1 by stating that R₁, R₂ and R₃ are each H. Claim 13 limits claim 1 by stating at least one of R₁, R₂ or R₃ may be an optionally protected substituent group, while claim 14 requires at least one optionally protected substituent group. Claim 15 limits claim 1 by stating that each X₂ is S. Claim 16 limits claim 1 by reciting several possible heterocyclic base moieties that may exist within the oligomeric compound. Claims 17 and 18 limit claim 1

Art Unit: 1635

by stating the length of the oligonucleotide is between 8 and 30 or 15 and 25. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Yau discloses a method of producing phosphorothioate oligonucleotides exemplified in scheme IV. The structures of the oligonucleotides produced by the invention are shown in columns 15-16 and through line 18 of column 17 and include oligonucleotides where the 3' nucleotide contains a phosphorothioate (if X is H); the heterocyclic base can be natural or synthetic (B_x is one of the moieties listed at column 17, lines 9-14). Yau discloses at column 6, lines 1-5 that oligonucleotides produced by the invention are useful in antisense methodology and would comprise between 10 and 30, preferably 15-25 nucleotides, meeting the limitations of claims 17 and 18. Although the oligonucleotides shown in the structure in column 15 are shown as DNA, Yau throughout column 5, beginning at line 23, states that

"Oligonucleotides according to the invention also can include modified subunits"

"The term oligonucleotide...refers to structures that include modified portions, be they modified sugar moieties or modified base moieties, that function similarly to natural bases and natural sugars"

"Representative modified sugars include...sugars having substituent groups at their 2' position,"

"All such oligonucleotides are comprehended by this invention so long as they function effectively to mimic the structure of a desired RNA or DNA strand"

Thus, Yau discloses oligonucleotides that meet the limitations of both claim 13 and claim 14. The structure disclosed by Yau at column 15 where X is H and n is 5 or more would, upon removal of the R group as described at column 10, lines 30-40, produce an oligonucleotide identical to that of claim 1 where T_2 is a phosphorothioate

Art Unit: 1635

monoester, each R_1 , R_2 , R_3 is H and each of X_2 is S, meeting the limitations of claims 1, 2, 11 and 15. Use of a nucleoside having a modified sugar in the process illustrated in scheme II, which is comprehended by the invention as described above, would produce an oligonucleotide that meets the limitations of claims 13 and 14. At column 6, lines 25-29, Yau discloses that the oligonucleotides of the invention can be formulated as compositions with a pharmaceutically acceptable diluent or carrier, meeting the limitations of claim 20.

Thus, Yau discloses all limitations of and anticipates claims 1, 2, 11, 13-18 and 20.

Claims 1, 2, 11-16 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Cook (US 5,521,302).

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at one terminus. Claim 2 recites that Q_1 is S, reciting a thiophosphate attached to a normal ribose sugar. Claim 11 limits claim 1 by stating that R_1 , R_2 and R_3 are each H while in claim 12 they are each OH. Claim 13 limits claim 1 by stating at least one of R_1 , R_2 or R_3 may be an optionally protected substituent group, while claim 14 requires at least one optionally protected substituent group. Claim 15 limits claim 1 by stating that each X_2 is S. Claim 16 limits claim 1 by reciting several possible heterocyclic base moieties that may exist within the oligomeric compound. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Cook discloses a method of producing oligonucleotides with chirally pure phosphorus linkages using synthons that contain optionally substituted phosphate groups. The structure of the synthons used in the invention are shown in columns 4-7 and include the option that the phosphate be a phosphorothioate (if R_d or R_e is S), the heterocyclic base can be natural or synthetic (B_x is one of the moieties listed at column 6, lines 33-36), the nucleotides can be DNA nucleotides (R_x is H) or can be RNA, possibly containing sugar substituents (R_x is OH or "a sugar derivatizing group). This structure meets the limitations of claims 11-14 and 16. Use of the disclosed synthons to produce oligonucleotides is illustrated in scheme 1. The synthons contain phosphate groups attached to the 5' hydroxyl of the sugar. Cook specifically contemplates the production of oligonucleotides containing 5' phosphate groups at column 16, lines 49-51.

The structure disclosed by Cook as structure 17 where the final R_d or R_e is S, at least one of the other R_d or R_e is S, R_x is H and n is 4 or more would upon removal from the CPG support produce an oligonucleotide identical to that of claims 1 and 2 where T_2 is H, T_1 is the modified phosphate group with Q_1 being S, each R_1 , R_2 , R_3 is H and at least one of X_1 is S.

The structure disclosed by Cook as structure 17 where the final R_d or R_e is S, at least one of the other R_d , each of the other R_e is S and n is 4 or more would upon removal from the CPG support produce an oligonucleotide identical to that of claim 15 where T_2 is H, T_1 is a phosphorothioate monoester and each of X_2 is S. Use of one synthon having R_x as a sugar derivatizing group produces an oligonucleotide that meets the limitations of claim 14.

Thus, Cook discloses all limitations of and anticipates claims 1, 2, 11-16 and 20.

Claims 1-4, 11-18 and 20 rejected under 35 U.S.C. 102(b) as being anticipated by Uhlmann et al. (US 6,033,909).

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at one terminus. Claim 2 recites that Q_1 is S, reciting a thiophosphate attached to a normal ribose sugar. Claim 3 recites that Q_2 is S, reciting a phosphate attached to a 5'- or 3'-thionucleotide. Claim 4 recites that one position of the modified phosphate is methylated. Claim 11 limits claim 1 by stating that R_1 , R_2 and R_3 are each H, while in claim 12 they are each OH. Claim 13 limits claim 1 by stating at least one of R_1 , R_2 or R_3 may be an optionally protected substituent group, while claim 14 requires at least one optionally protected substituent group. Claim 15 limits claim 1 by stating that each X_2 is S. Claim 16 limits claim 1 by reciting several possible heterocyclic base moieties that may exist within the oligomeric compound. Claims 17 and 18 limit claim 1 by stating the length of the oligonucleotide is between 8 and 30 or 15 and 25. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Uhlmann et al. disclose oligonucleotides having the formula shown in claim 1. In this formula, the internucleotide linkages can be mono- or diphosphorothioate, meeting the specific limitations of claims 1 and 15. The V at the 5' position of the ribose can be O or S and the terminal R^1 can be a phosphate or thiophosphate group, which is the equivalent of the structures of claims 1-3 wherein T_1 is a modified phosphate and one of Q_1 and Q_2 is S. Also, the Y' at the 3' terminus can be S attached to a phosphate group,

Art Unit: 1635

which is the equivalent of the structures of claims 1-3 wherein T_2 is a modified phosphate and one of Q_1 and Q_2 is S. The Z position of the terminal phosphate groups can be C_1 - C_{18} alkyl, meeting the limitation of claim 4. In the oligonucleotides disclosed by Uhlmann et al., R^2 can be hydrogen, hydroxyl or other substituents, meeting the limitations of claims 11-14. Position B is disclosed as being a conventional nucleotide base, meeting the limitations of claim 16. The oligonucleotides of Uhlmann et al. are 2-101 nucleotides in length, meeting the limitations of claims 17 and 18 and are disclosed in claim 9 as compositions with pharmaceutically acceptable carrier or diluent, meeting the limitations of claim 20.

Thus, Uhlmann et al. disclose all limitations of and anticipate claims 1-4, 11-18 and 20.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Art Unit: 1635

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
November 7, 2006

A handwritten signature in black ink, appearing to read "Tracy Vivlemore", is written over the typed name and title.